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COMMENT

The innate immune system: gatekeeper to the female reproductive tract

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Sexually transmitted diseases (STDs) are a major worldwide health problem that compromise reproductive fecundity as well as cut short the lives of millions of men, women and children.[1,2] Despite extensive efforts, only limited success has been achieved in dealing with STDs, including herpes simplex virus type 2 (HSV-2), *Chlamydia trachomatis*, group B streptococcus and human immunodeficiency virus [(HIV), the causative agent of acquired immune-deficiency syndrome (AIDS)],[3] which collectively devastate both adults and newborns. It is now well recognized that the heterosexual transmission of HIV, which is reponsible for 70–80% of the new cases identified in the last 2 years, is the major route of infection worldwide.[4,5] With the identification of HIV in semen and cervical secretions,[6–8] AIDS is now the major life-threatening STD.[9,10] As strategies are developed to prevent and effectively treat this growing global health problem, understanding the immune system in the female reproductive tract and the way it is regulated by the endocrine system has particular importance.

The adaptive and innate immune systems are the two key branches that determine host protection throughout the female reproductive tract and at other mucosal surfaces, including the respiratory, gastrointestinal and urinary tracts. Adaptive immunity encompasses the recognition and response to antigens with resultant protection that is gradual, very specific and mediated through antibodies and/or T cells. In contrast, innate immune responses use non-specific mechanisms that are inherent, rapid and mediated by germline-encoded receptors.[11] Our understanding of the innate immune system is a result, in large part, of the pioneering studies of Charles Janeway, who demonstrated that innate immunity covers many areas of host defence against pathogenic microbes.[12] During the last decade, investigations of the innate immune system have shown that microbial pathogens are recognized by Toll-like receptors that, in turn, regulate the activation of both innate and adaptive immunity.[11]

Mucosal surfaces have evolved to handle potential pathogens against a background of selective physiological functions. In the reproductive tract, the immune system must balance the presence of a resident population of bacteria in the vagina with periodic exposure in the uterus and Fallopian tubes of antigens (bacteria and sperm), as well as the long-term exposure of an allogeneic fetus. Failure of the immune system either to rid the reproductive tract of potential pathogens or to resist attacking allogeneic sperm and fetus significantly compromises procreation, as well as the health of the mother. To meet these diverse challenges, the immune system has evolved to be precisely regulated by the ovarian hormones oestradiol and progesterone, which prepare the reproductive tract for successful fertilization, implantation and pregnancy.

In the current issue of *Immunology*, the article by MacNeill *et al*.[13] collectively extends our understanding of the complexity of the innate immune system that has evolved to confer protection against potential pathogens. Previous studies have demonstrated the essential role of Surfactant protein A (SP-A), a member of the collectin family of proteins, in protecting the respiratory system from infections. SP-A gene knockout mice are more susceptible to bacterial and viral lung infections than their wild-type counterparts.[14] The findings of MacNeill *et al*., that SP-A is expressed in the vagina, demonstrates the existence of a new molecule in the reproductive tract that is important in host defence. As discussed in their article, SP-A has the ability to facilitate phagocytosis of micro-organisms, stimulate chemotaxis, increase the oxidative burst by phagocytes and modulate pro-inflammatory cytokine production by immune cells.[15–17] Moreover, SP-A has been shown to regulate the differentiation and chemotaxis of monocytic cells, including dendritic cells, to provide a link between innate and adaptive immune responses.[18] Of particular importance is the growing body of evidence demonstrating that SP-A binds to a diverse range of Gram-negative and Gram-positive bacterial and viral pathogens,[19] providing for effective killing and/or opsonization by phagocytic cells.

Innate immunity utilizes a spectrum of molecules to confer protection against potential pathogens. One example is the production of soluble factors by female reproductive tract epithelial cells that inhibit the growth of micro-organisms. Among the epithelial cell secretions with known bactericidal effects are defensins, secretory leucocyte protease inhibitor (SLPI), the enzymes lysozyme and lactoferrin, as well as other antimicrobial peptides (reviewed in ref. 20). While research in a number of laboratories has demonstrated sex hormone

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regulation on multiple aspects of the adaptive immune system (reviewed in refs 21 and 22), we have only begun to explore the hormonal regulation of innate immunity in the female reproductive tract. What is clear is that epithelial cells from a variety of tissues produce defensins, particularly β-defensins.[23] The synthesis and/or release of these 'natural antibiotics' may be constitutive or rapidly induced by infections or toxins, and, in general, they act via their amphiphilic charge on the microbial membrane to create pores or otherwise affect permeability. These ubiquitous antimicrobials are effective against Gram-negative and Gram-positive bacteria, fungi and some viruses. Human β-defensin 1 is produced by the epithelial cells of the female reproductive tract[24] and has a primary role in defending mucosal surfaces against microbes.[25] Human β-defensin 1 is primarily constitutively produced, whereas human β-defensin-2 is usually induced by infection. Zhao and colleagues[25] suggested that human β-defensins have a primary role to defend epithelial cells and mucosal surfaces from microbes, while α-defensins function systemically to allow immune cells access to vascularized tissues.

Recent studies suggest that, as with the adaptive immune system in the female reproductive tract, some components of the innate immune system are under hormonal control. For example, the level of human defensin-5, an α-defensin produced by endometrial epithelial cells, is highest during the secretory stage (postovulatory) of the menstrual cycle.[26] SLPI is produced by macrophages and epithelial cells, including those in the female reproductive tract,[27] and has broad-spectrum activity against a variety of potential pathogens,[28] including HIV-1.[29,30] Levels and/or expression of SLPI vary in cervical mucus during the menstrual cycle (but not in serum)[31,32] and increase in amniotic fluid during gestation. King and associates showed that the primary site of SLPI synthesis in the endometrium and decidua was the glandular epithelium, and tissues derived from women in the late secretory phase produced higher SLPI levels than tissues obtained from women in the proliferative phase.[33] In our laboratory, polarized monolayers of uterine epithelial cells from premenopausal women secreted more SLPI than did cells from postmenopausal women.[34] When bactericidal activity was analysed, Gram negative and Gram positive bacteria were inhibited by apical secretions from uterine epithelial cells. As antibacterial activity was neutralized by antibody specific for SLPI, the antibacterial activity demonstrated by the human uterine epithelial cells is probably a result of the presence of SLPI, the secretion of which is dependent on menstrual status.

In summary, understanding how the immune system in the reproductive tract responds to bacterial and viral challenges requires that we identify the unique characteristics of the immune system in the Fallopian tube, uterus, cervix and vagina, and the ways in which the innate and adaptive immune systems are either enhanced and/or suppressed by sex hormones at particular times in a woman's life. Studies like those of MacNeill *et al.*[13] provide important new information that extends our knowledge of immune protection. These studies and others like it should provide the basis essential for the prevention of local infection in the genital mucosa and the management of sexually transmitted diseases.

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